done as an extra arm and when you have -- but the comparison was done to the control group in the open study. When you do that, you've got to be very careful. And here I think we haven't been so careful because I do think there are differences between the patients. It was minimized, I think, at various points, but there are differences if I read it right and, of course, again, I'm just a statistician so I might not have read it right.

But if I understand right, the laparoscopic patients had less previous back surgery. What does that mean to me? Well, they haven't been in to the doctor so much. I mean, that's good. They're maybe at an earlier stage because they're on more non-narcotic as opposed to strong narcotic medications. Okay. They have better pre-op neurological scores, better SF-36 MCS scores, better leg -- they look like they're a healthier population, just from my perspective as an unbiased -- well, I think I'm unbiased, as a statistician looking at it, how is that? I'll say that.

Now, if you have differences in a group

and you want to make a comparison to control and you have differences of some sort, you really should think about making some adjustment for that and I didn't see any adjustment. So that's a question I have. The results look very good. In fact, in some cases, they're called superior but I don't think any of those analysis I know of made adjustments for perhaps that the laparoscopic patients were better to begin with. I don't think that happened.

So with respect to laparoscopic, I think we're in a situation where there is a possibility that an adjusted analysis would change the conclusions somewhat but I don't feel, given they had reasonably good results, I don't feel it would change it so much that we should discard the good results we have. You do have some what I would say advantage there because at least the laparoscopic patients that were better turned out to do better, that's at least comforting. But I do think an adjusted analysis might give us a slightly different story there. And so on that note, I think I'll stop.

Thank you.

CHAIRPERSON FINNEGAN: Thank you. That was, as usual, very enlightening. What we're going to do now is I'm going to ask Aric to put up the questions and then we're going to go around the panel and I'm going to ask each panel member with their expertise and their comfort level, to discuss their concerns, questions and perhaps, some thoughts they have on what's been presented so far, and just to warn you, Stephen, we're going to start with you.

DR. KAISER: Okay, as I mentioned earlier, we've got some general topic areas where the questions are coming from and as we move into the first area, reproduction, teratogenicity, we have several questions that we would like you to discuss in this area and would you like me to go through all the questions in the topic and then come back to the beginning? Okay.

In this area, the first thing we'd like you to do is discuss the potential for an immune response in the mother to effectively block BMP-2 expression in the developing fetus. We'd also like you to discuss the potential that the fetal expression

of BMP-2 could restimulate a maternal immune response and cause adverse effects in the mother.

I'll go back to the first question.

CHAIRPERSON FINNEGAN: Actually, I'm going to have you run through them all, all the questions.

DR. KAISER: Okay, all right, the next category, tumorigenicity, we'd like you to discuss the potential for rhBMP-2 to stimulate growth of transformed cells. Now, I want to mention and it's been mentioned previously that this category and the previous category are based on potential issues, hypothetical issues. These were not things that were seen in the clinical data set presented by the sponsor but these are things based on information from the literature that could happen in the presence of the growth factors.

Okay, next radiographic effectiveness and this is a question that comes actually from the data presented by the sponsor. Given what you've seen from the sponsor data and from our presentation, we'd like you to comment on interpretation of the radiographic findings at various time points in view of the

following factors; the presence and resorption rate of the collagen sponge, the carrier for the BMP, the progression of bone repair in the presence of rhBMP-2 in the case of the investigational patients and the absence of rhBMP-2 in the control patients and the relative ability of bone formed at various time points to withstand the applied loads.

Now, we move onto some things that based on the data we'd like to get some input on some of the labeling issues with this product. The first thing, with respect to instructions for use, we'd like you to provide some suggestions for adequate instructions with respect to the radiographic interpretates, so based on the previous question if there's anything that we should be putting in the labeling.

In addition, we'd like you to discuss any other specific training that should be implemented with respect to this product. We have a number of questions that are related to post-market studies. The first has to do with reproduction in teratogenicity. FDA believes that additional animal studies may be useful for assessing an immune response

effect on fetal growth and development and so we'd like you to comment on the need for these studies. If you decide that these studies are necessary, the types of studies that should be performed as well as appropriate animal models.

In the area of tumorigenicity, we've described and the sponsor has described that there's been an agreement to conduct some additional studies -- additional non-clinical studies to evaluate potential for rhBMP-2 to stimulate transformed cells. And what we would like you to do is comment on whether there are any additional studies beyond those ones that we've already agreed to, to address this issue and if you believe that there are, we'd like some comment on the type of studies to be performed as well as the appropriate animal models.

And then finally we'd like to have your comments on the use of ongoing post-market registry data bases to further assess potential for congenital abnormalities. And as with the previous two questions, if you believe that registries are recommended, we'd like to have some input on the types

of data to be captured.

CHAIRPERSON FINNEGAN: Okay, thank you. Just to clarify for the panel, I would like you to give your opinions. If you have questions for the sponsor, you might give them a heads up but we're going to go around a second time with specific questions for the sponsor, so this is mainly a generic discussion of your concerns and any thoughts you have on the questions. Dr. Li.

DR. KAISER: I'll leave this first question up and then let me know when you want me to pop to the next one.

CHAIRPERSON FINNEGAN: I think we've got a copy.

DR. LI: Yeah, my materials and engineering background doesn't exactly equip me to answer this question directly. A heads up maybe to the FDA or experts or the sponsor, I guess my question would be, are there any examples of any agent, pharmaceutical or otherwise, that actually passed all the in vitro tests that you've done on tumorigenicity or teratogenicity or the other things that you've

tested that actually in vitro did not cause any ill effects but actually turned out to actually have a clinical effect? Because if the answer is yes, then I'm really stuck with this question.

CHAIRPERSON FINNEGAN: Dr. Doull.

DR. DOULL: Yeah, my question is peripheral also, and it's a heads up. When Dr. Hudson was talking about BMPs he mentioned the fact that there's a lot of variability in specie sensitivity to these agents. That also was brought up a couple other times and it's in our book and my concern is usually when you have intraspecies variability like that, you also -- or interspecies variability, you usually also have intraspecies variability. Yet, as I understand it, you're talking about taking a vial of this material, a standard dose, diluting it up, putting that on the sponge and putting it in the cage and it's the same dose for everybody; old, young, male, female, whether they are immuno compromised.

And if that's true, it makes it a little hard to look at the worst case kind of assumption that one would like to make to evaluate systemic toxicity

as opposed to local toxicity.

CHAIRPERSON FINNEGAN: Dr. Diamond?

DR. DIAMOND: I guess my concerns have to do with the antibody assays because I'm concerned that they represent arbitrary numbers with a definition of authentic response but no definition of a biologically significant response and I think that, you know, one doesn't know what a neutralizing antibody titer is and -- unless there are studies that haven't been done and we certainly do know that antibodies, maternal antibodies can cause problems in a developing fetus and the IgA antibodies may not get across the placenta but they certainly get into milk and get into neonate. So it's about the antibody assay.

CHAIRPERSON FINNEGAN: Dr. Hanley, sir.

DR. HANLEY: Yes, I'd like to preface my comments by saying that I've been to many of these meetings before and served as the chair of many of these. I'm a non-voting member at this meeting because of my previous involvement in studies on the spine and particularly in some of the initial studies with BMP use on the spine prior to what is going on

here, some with Genetics Institute but not with the current sponsor Medtronic Sofamor Danek.

Several years ago we had a meeting of the Food and Drug Administration Orthopedic and Rehabilitation Advisory Panel with regard to spinal conditions in an attempt to set some criteria such that sponsors would have a good idea of what was needed for us to pass scientific judgment on what they did. Heretofore, I have personally not seen studies put together in a fashion that we could do it well.

I would compliment the sponsors on meeting all the criteria which were set down several years ago and I don't know if anyone's here who participated in that but what they have done is exactly what we've asked people to do so that we could make our job easier and not spend all afternoon saying, "What did you mean by that", or trying to make up for things that weren't there.

So I applaud them on their issues. I'm a spine surgeon, a clinician and I view myself as reasonably knowledgeable with regard to the issues; spine surgery, the selection of patients, the

performance of the procedures and the use of the implants and materials under discussion here.

We will not and cannot solve the enigma of back pain in the selection of patients for surgery for it here. It is not part of this discussion. I do not believe that radiographic issues brought up have great pertinence to this presentation. They are what they are and our opinions on what's better if any of CT, regular radiograph, bears not on -- in my opinion, on decisions that should be made here. Those are part of the clinical practice.

It's nice to see that they included CT. It just means they're trying to give us everything that could be meaningful but I don't think it matters in the long run if the device is deemed to be approved and is approved, that the criteria be set up for what a practicing clinician should do.

That's a study issue. I'm sure plain radiographs are just as satisfactory and the patients, ultimately if this were approved, operated on with a device that should not be -- need not be subjected to CT unless for specific instances such as a clinical

failure.

Some of the other things that might not be apparent to non-clinicians are issues like blood loss and blood loss is so small in all the groups that it makes no difference. The length of stay, however, has some import and this is one time where not taking a bone graft probably does dramatically improve the length of stay issue, particularly in that other arm that we criticized a little bit, laparoscopic arm.

I'm not an expert on teratogenicity and tumorigenicity and that sort of thing. I think we'll let others who have more expertise work that out. I think the issue here at the table today is mainly one of labeling, indications for use, trying to put in the proper perspective for -- if approved for people utilizing a device, how best it can be controlled and doing some appropriate follow-ups on it. This is -- it's been a good experience, one of the easier ones I've seen. Thank you.

CHAIRPERSON FINNEGAN: Gene.

DR. SIEGAL: Well, if there's a good cop, I guess there has to be a bad cop, too.

CHAIRPERSON FINNEGAN: You said that with a smile.

DR. SIEGAL: I have a number of issues. I do think that the sponsor did everything that reasonably could be done as far as the radiology, especially by acquiring the expertise of Dr. Genant and his associates, who is a world renowned authority and I feel very confident that everything that could be done radiologically has been done. However, histology/pathology has been eluded to multiple times, both in the pre-clinical and the clinical.

And it was used as the gold standard, if you will, to validate the radiology. I have a multi-part question depending on the answer and the question goes something like this. Were those veterinary or human pathologists that did those studies, neither or both? Did they work for the company or was there an independent vetting of the pathology results? Were the pathologists recognized as experts in bone diseases?

Changing subjects, as I understand the carcinogenicity issues, two pancreatic cell lines

showed increased proliferation in the presence of BMP-2 and one patient developed pancreatic carcinoma while receiving the therapy. I would like to hear that coincidence or a potential problem. I wonder too, way off the topic perhaps, that at the time of surgery, the rhBMP-2 must be rehydrated, if I could use that term, with sterile water and then must be, quote, "applied evenly" end quote to the ACS which is loaded into the cage. Why was it not discussed pre-loading the BMP-2 sponge to maximize even distribution, either requiring hydration by perhaps emersion in water or pre-hydrating it and packaging it to keep it intact?

And to come full circle back to the pathology question, I wonder would it not be of value to do a carefully controlled radiology histopathology study with pathologists to see, in fact, if there is a gold standard one against the other?

DR. KIRKPATRICK: I'd like to echo some of the other panel comments, that that was quite a well-prepared presentation and a substantial data set to review. A few questions that I'd like to see addressed are, you mentioned that you have data beyond

24 months. How complete is it and did you see deterioration in the clinical results which is something that we often see with other fusion techniques?

I would like to see if you could provide me with some general insight with the expression of BMP-2 normally in the time course of the fusion. In other words, do we have any information on when BMP is normally produced in the fusion healing process and whether the application of the BMP-2 at the onset is coincident with what it would be in the autograft group, for example? I imagine you already have that data.

You mentioned that the metabolic pathway of BMP was through the liver but I did not hear a specific of what that pathway was in the liver and the package insert, as I recall, indicates that no liver studies were done. I'm wondering since one of your explanations about the toxicity was the fact that it was rapidly metabolized, what liver impairments would prevent it from being rapidly metabolized and as such, what liver enzymes should be checked prior to giving

the device or using the device.

And the next question is perhaps one, if we find it approvable, in light of the history of the pedicle screw off label use, how would you recommend guarding against off-label use of this product, especially the rhBMP-2? Thank you.

CHAIRPERSON FINNEGAN: I basically have two areas that I would sort of like to see discussed. One is there were some very nice elution studies of the BMP but you didn't look at elution or I didn't see any data for elution from -- of the BMP inside the cage and I would suggest that that's probably a different pattern than just BMP in a sponge.

And the other thing that fascinated me that I couldn't find anywhere is why did the cases that failed fail. You picked pretty straightforward pretty simple spine problems and I was wondering if you have any feeling for why the ones that failed failed.

DR. NAIDU: I'd like to comment -- congratulate the sponsors for doing an excellent outstanding study. I thought it was very well

presented. The data showed that the device is effective and with regards to safety, I will hold on. I'm an orthopedic surgeon with a biomechanics background. I will defer that question to the biologists on the panel, but in general, from what I've heard at least, the antibody response was detected in only three of the patients and from Dr. Miller's comments, it appeared as if hardly any cross the placenta barrier nor the amniotic cavity and our respected panel member, Dr. Reddi, goes on to comment that this is a normal substance. We should not be too concerned about it. And so I will defer that thought to Dr. Reddi and the rest of the biologists on the panel.

But as far as the radiographic findings, I think that it appears as if at least from the CD Roms, the CDs that I got, the disks, the fusion mass started to show up at six months as the sponsor stated, and the thing is I don't have any time zero CT scans to judge as to what it would look like. I can only imagine the collagen sponge would be hollow and it would be black. It would only be logical to assume

that. So I think that there is bone forming, but I don't know the mechanical integrity of this bone.

And Dr. Kostuik stated that at least eight millimeters of bone must be needed to -- a thick -- eight millimeter thickness of bone must be needed to stabilize an intersegmental fusion. And the other thing is in light of Dr. Kostuik's comments where he stated that it is hard to judge on flexion/extension views mainly because of the superior instrumentation that we have developed today, such as segmental spinal fusion devices such as pedicle screws, it's hard to depend on flexion/extension views. Those are the words that I recall from Dr. Kostuik.

These are not -- you don't have pedicle screws here. You just have two cages. And so I would assume that the flexion/extension criteria that you guys used would be credible at least. That's what common sense would dictate to me at least. But I think that's all to an issue to discuss further is just the stability of these devices. Are they similar to these pedicle screw constructs that flexion/extension views and angular distortion is not

considered credible as a radiographic criteria.

I think that you guys have shown a pretty reasonable product here that seems to be safe and efficacious but obviously, there are some issues as far as packaging and I'm also assuming that -- this is actually a question to the sponsor, that you are seeking approval for this for degenerative disc disease with less than grade one spinal disc thesis (ph) for single level fusion. That's what I'm assuming that this device is up for. If I'm wrong as far as that goes, I would appreciate clarification but thank you very much.

CHAIRPERSON FINNEGAN: Dr. Boyan.

DR. BOYAN: I have just two issues that have come up in my reading of the documentation and the discussion today and overall I, too, want to compliment the applicant. It truly was a beautiful package to read, but the two comments I want to make have to do -- one with mineralization and the other one has to do with antibodies.

And the mineralization has to do with how the use of CT and x-ray. I would like to echo the

comments from down at the end of the table that it's very difficult at least early on to determine whether or not something is bone or if it's just remineralized collagen and given that you're using a collagen sponge, even x-ray or CT isn't able to discern whether or not that's bone, bone or if it's a graft that was fortuitously structurally remineralized.

And I say that only as informational because the only way you could ferret that out is with histology and you're not likely to take a nicely fused human and do histology but to bear that in mind in interpreting the data. The other comment has to do with antibodies and while I may not be as concerned as some people are about this future consequence to a pregnant person and her fetus, I am somewhat concerned about elderly individuals and people who are likely to have more than one experience with this device in their lifetime.

And if there has been any consideration given to people that might have multiple surgeries at different times and whether or not we're sensitizing them to be BMPs and sensitizing them to type 1

collagen.

CHAIRPERSON FINNEGAN: Thank you. Dr. Reddi.

DR. REDDI: Yes, thank you for giving me this opportunity, Madam Chairman. First, I'd like to also compliment the sponsors for giving us a good package but however, I have some questions which I was not sure whether I should outlay while I made a brief presentation or not because I'm a novice at this but I will very soon learn.

But I would like to ask as far as the tumorigenicity is concerned, whether the sponsor or some of their contractors have done studies because we are really interested in induction of tumors as opposed to stimulating growth of transformed cells. I found copious amounts of data on about 60 cell lines. A lot of cancer research today in the United States has shied away from cancer research because it doesn't mean anything for the human patient, because you can get whatever you want in a cell line, it might please some FDA regulators, but we are really -- it's a very important issue from the point of your patient.

If you really want to study tumorigenicity, it needs to be done in a living animal and I wanted to find out if such attempts are being made or being thought about by the sponsor, so I'd like to find out whenever the time is opportune for that.

The other question concerning the antibodies, I wanted to find out if the sponsor in their volumes of study have developed antibodies to the native BMP-2 as opposed to anti-peptide antibodies or monoclonal antibodies because you might make an antibody to a peptide by one of the scientists in Wyeth-Genetics Institute but I would like to see if there is such data and if such data is available, I would like to strongly recommend that the transplacental passage of these antibodies to native recombinant BMP-2, does it cross and does it have any adverse effects on the fetus.

That's a very important thing because we have been dancing around this issue. I think we need to do definite studies in order for both the -- to allay the fears of both the patients as well as the

surgeon.

CHAIRPERSON FINNEGAN: Thank you. Now we're going to get a definitive answer about x-rays and CT scans, right?

DR. LENCHIK: I thought we were still talking about teratogenicity. I don't have much to say about that but to your preview, the sponsor, I have a couple of questions relating to CT. The CDs that we were given, the quality of the CT really varied widely from having real quality CTs with beautiful coronal and sagittal recon to other CT scans that were virtually uninterpretable.

So my question to Harry Genant in particular is what was your experience in the study in terms of CTs that were potential equivocal because you couldn't -- because of metal artifact perhaps or due to reconstruction artifacts. And the second question, again to the sponsor, what do you think the explanation is why there were fewer patients fused by CT at 24 months compared to 12 months?

CHAIRPERSON FINNEGAN: Dr. Larntz?

DR. LARNTZ: I don't have any more to add

than I already did.

CHAIRPERSON FINNEGAN: Ms. Rue?

MS. RUE: I have a couple questions. They're points of discussion I guess. One was there was an agreement made with the women in the group for them not to get pregnant and they talked that there were six pregnancies anyway, not to get pregnant for 16 weeks and it doesn't say at what time these women got pregnant. So I'm wondering what effect that agreement held.

And also, if there's going to be a pregnancy registry board, that it include miscarriages of the fetus or embryo at any stage and also some pathology on that to see if there's any effects on the fetus. And also, the fact that the majority of pregnancies are not planned and most women don't know that they are pregnant for the first at least five to six weeks, a lot longer than that, what is going to be done as far as that goes prior to surgery.

CHAIRPERSON FINNEGAN: Thank you. Ms. Maher?

MS. MAHER: I don't have much to add above

and beyond what everybody else has said and I thought what I heard was very well put together. I would ask the panel to be cautious about trying to mandate the practice of medicine as you're going forward and talking about labeling that would determine when fusion has occurred. I think most surgeons know when fusion has occurred and will be making that determination on their own no matter what's in the labeling.

So I would ask us to all be cautious and think about that. I would go the same way towards the concerns about off-label use. I think labeling can go into the labeling but there's -- mandating packaging or something like that will increase the cost of the product to the consumer without probably stopping much of what you're probably trying to stop. Thank you.

CHAIRPERSON FINNEGAN: All right, we'll now start back around the table and you can ask your questions and we'll get them to answer them one at a time. Dr. Li.

DR. LI: Do I ask the same question?

CHAIRPERSON FINNEGAN: Yeah, the same

question or a new one if you have another one.

DR. LI: Yeah, I guess my original question was, if you've done a variety of in vitro tests to test tumorigenicity, teratogenicity and other possible complications. My question actually was either the sponsor or the FDA or panel members, are there examples of any agent that actually would pass all these tests, yet turn out to be clinically something you'd want to avoid?

In other words, how -- the fact that you passed all these tests, is that actual assurance that these things will not happen clinically?

CHAIRPERSON FINNEGAN: I don't know who the most appropriate -- probably, Dr. Riedel, did you want to answer that or did you --

DR. RIEDEL: To the best of my knowledge and the knowledge of my colleagues who are professional toxicologists, there is no example of such an agent. It would be just hypothesize.

DR. LI: Okay, my question did ask earlier because I was limiting myself to teratogenicity, was on the x-rays versus CT. I guess my question on that

is, was the determination of whether or not there was a bone bridge, is that just a yes or no determination? And if it was just a yes or no determination, there's like one spicule or one trabecula that goes from side to side, does that count as a bone bridge or was there some threshold amount of bone that had to be in there to be qualified as a bone bridge.

And a follow-up question to that is, no matter how you determined whether or not it was fused or not fused by radiographic approaches, how predictive of clinical failure were those radiographic approaches? For instance, were there cases where there was a radiographic failure but the patient was perfectly happy with it and conversely, were there clinical failures that radiographically looked great?

CHAIRPERSON FINNEGAN: I think, Dr. Miller, did you want to address the question about whether there's been an example of -- in something not showing any signs in vitro but turning out to have some effects in vivo?

DR. MILLER: Thank you. Some of the estrogens might fall into that category, being diethyl

stebesteral (ph) originally and probably that might be out closest that we might look at along those lines both being tumorigenitic birth defects and for quite awhile one didn't have that understanding because the right tests weren't done but --

CHAIRPERSON FINNEGAN: So there is at least one example. All right, Dr. Doull, did you want to ask your question?

DR. GENANT: Can we answer?

CHAIRPERSON FINNEGAN: Oh, yes. Well, actually, I think that was -- oh, radiographic, I'm sorry.

DR. GENANT: I'm Harry Genant from the University of California, San Francisco. I have no vested interest in the product and I'm a paid consultant. I've also been a consultant with Ostech in the past.

Now, with regard to the predictability of the radiographic features, that is either plain films or the CT in relationship to success, we have to keep in mind here that at 24 months we did have a very high success rate. And so we're talking about relatively

small numbers of cases. The majority of those cases that were re-operated were not re-operated specifically with the suspicion that they were, in fact, unstable, but rather related to other symptoms and findings that were being addressed.

So I would say that there was not a strong or tight correlation in those small cases between the radiographic and/or CT features of fusion and the presence, for example, of a need for re-operation.

DR. LI: Were there cases where there appeared to be radiographic failures either by x-ray or by CT but were clinically -- had no complications?

DR. GENANT: There were cases in which lucencies had been observed in which there were no clinical manifestations. Thank you.

DR. LI: Thank you. Oh, yeah, the issue about how you determine whether or not there was bone bridging.

DR. GENANT: Yes, the question with regard to the amount of bone that might be relevant for bridging and in particular based upon the CT observations, I would point out that by 12 and

particularly by 24 months, one observed not only the bony bridging within the cage, but in the majority of cases one observed also substantial bridging of bone either in front, behind or on the sides adjacent to the cage.

I'm not certain that we made a determination of what the minimum amount for thickness of the bridging would be necessary in order to consider this to be clinically relevant, but we essentially made the assessment of whether we could judge there to be solid bony union across either within or outside of the cage.

DR. BODEN: I just want to expand one point about the dissociation between radiographic outcome and clinical outcome which I believe was the subject of your question. It is not at all uncommon in treating patients with spinal disorders, particularly patients that have so-called degenerative disc disorders, which is the subject of these patients, to have solid fusions yet persistent symptoms or cases where symptoms improve and it doesn't correlate with the radiographic outcome.

So that's inherent with the disease, the disorder and even accomplishing a fusion by any means independent of whether it uses bone graft or infuse. That's particularly why it's important to focus on the more direct or primary outcome and goal of something like infused, which is to generate bridge in bone. When you start to add the overall success factors, there's a lot of other things multi-factorially that go into that that go well beyond the device in question.

DR. LI: So you're saying that the -- if I understand what you told me, that the presence of bridging bone is not just a biomechanical benefit, but it's actually a reflection of other things that are going on with the device?

DR. BODEN: No, I don't think that I was trying to say that at all.

DR. LI: Okay, sorry. So let me follow, just maybe to pinpoint this again; do you have any correlation from animal data or any other data that correlates the amount of bridging bone in any biomechanical measurement; torsion, strength, failure?

Is there any number that you --

DR. BODEN: Well, we showed -- we showed in the cases of the animals that the biomechanical properties of those fused segments were equal to or greater than those with autogenous bone graft at the same point in time and so, if anything, there's a trend to possibly achieving bony union a little bit faster and more consistently with infused compared to with autograft. Unfortunately, there's -- the fusion can occur through the center of the cage, which is typically the way it occurs with autograft and is considered clinically to be mechanically solid and solvent.

There's no clinical definition in humans of how much bone is enough bone. It's empiric. However, I will say that it tends to be a more than all or none response and I think that kind of case that Dr. Kostuik highlighted where there was some bone but it turned out to be not good bone, is more the exception than the rule and we tend to clinically think of fusion as a binary event, either solid bridging bone and then it remodels because of

continued mechanical stress whether that bone was put there by autogenous bone graft or InFUSE actually wouldn't effect the ultimate remodeling.

And so on the other hand, the clinical problem is you never get that union of bone. It never sees load and then it never remodels. Does that help clarify?

DR. LI: Yes, thank you.

CHAIRPERSON FINNEGAN: Go ahead.

DR. GENANT: Yes, I wanted to address the question that Dr. Lenchik had.

CHAIRPERSON FINNEGAN: Well, we'll get around to him in a second.

DR. GENANT: Oh, okay, it was relevant to this topic with regard to the --

CHAIRPERSON FINNEGAN: All right, go ahead.

DR. GENANT: And that was with regard to the CT and the quality of the images that were reviewed, and I sympathize with you to some extent with regard to the review of the CDs. I think that in most cases they were representative of the studies

that we looked at with the direct hard copy images but on the other hand, in some reproductions they did not capture the original image quality.

I would say that overall the CT quality of the images that we viewed were reasonable. There was some range in that quality but I think by and large, were acceptable for most -- the vast majority of cases and of course, we had, in general, excellent radiographic imaging.

CHAIRPERSON FINNEGAN: Thank you. Dr. Doull.

DR. DOULL: Well, as you know, in order to answer the question about safety, you need to ask whether the quantity and the quality of the tox studies were sufficient to provide one the ability to be reassured about safety and as I indicated, we have two kinds of safety questions here. There's the systemic toxicity and the local toxicity.

I think in terms of these studies, they were well-described and well-done. The doses looked fine and they are standard studies, so that I find those reassuring in regard to the systemic safety.

I'm not exactly sure what additional studies you're talking about that you might do to focus on the question of local toxicity transformation and so on.

DR. RIEDEL: If I can respond to that question, Dr. Doull. This is Gerard Riedel speaking. You had raised earlier the question of intra-species variability raising the issue of -- I'm sorry, inter-species variability raising the issue of intra-species variability and if I might, I'd like to address that question first --

DR. DOULL: Fine.

DR. RIEDEL: -- because I think it is relevant to this question. What we have observed is that it is the local concentration of BMP-2 applied on the absorbable collagen sponge which correlates with efficacy within a species and that that efficacy which is defined by that local concentration is consistent across all the anatomic sites where we've tested it in that species, and is independent of the total volume of the material that's implanted or in other words, independent of the total volume -- of the total dose of BMP that's implanted at that site.

A more specific application -- example is the following. If we implant rhBMP-2 in critical size defects in long bones or in periodontal defect pockets in a canine what we have found is that the optimal therapeutic concentration of BMP-2 on the sponge is identical in those two anatomic sites, but of course, the volume that's implanted in those two bony defects is very different. So that's the empirical observation.

Then to address the question about how does one appropriate dose in order to assess local toxicity, what we took was the strategy that we -- we tried to use as high a concentration as was feasible in terms of manufacture. And in the case of the rat implant toxicity study that I described to the panel earlier this morning, we applied a concentration of BMP-2 to the absorbable collagen sponge that was four milligrams per mil. That's the highest we can manufacture and put on the sponge.

Now, that's in excess of the concentration that's used in the human clinical setting which is one and a half milligrams per milliliter. However, it is

somewhere between 40 and 80 times in excess of the optimal therapeutic concentration in rats, which is somewhere in the range of 50 to 100 micrograms per milliliter. We took this approach in order to drive the concentration in order to look for some effect of cellular abnormality or toxicity at the local site.

So we didn't take a total mass of protein to total body weight approach, but rather this local concentration approach and that's the approach that we took.

DR. DOULL: You're on the low end below the threshold for a lot -- in the net conclusion of all your tox studies was no effect and that conclusion of many of your pharmacology studies were no effect, which, I guess it's a little hard to talk about therapeutic index for those kind of things, but that's, I guess the way the ball park is.

DR. RIEDEL: Your observations are correct. We tried very hard to find dose-limiting toxicity doses. We were unable in any of our studies no matter how high we drove the dose to identify a dose limiting toxicity.

DR. BODEN: Can I add a word about the intra-species variability or inter-species variability?

CHAIRPERSON FINNEGAN: Certainly.

DR. BODEN: Stated another way, the definition of the minimally effective dose for any given species was the dose which took out of play and intra-species variability. In other words, it was defined as the dose that would yield 100 percent consistent response in that species. And because there is a pretty wide range of therapeutic excess, in a sense, if you lower the concentration below what we've defined as the minimally effective concentration for a given species, you will see animal to animal variability but the way those are defined for each species is to take that out of play.

DR. DOULL: I was struck by our BMP experts. They're all telling us about the variability and sensitivity of different organs, of different cells, for example, and it just seems that that kind of variability between species, between cells, between -- that surely there must be a little difference

between an immunal compromised patient for example, what she really needs.

What you did in the rat was figured out how much you need in order to get that bone response and what is the maximum that increasing the dose no longer increases that response, which gives you that nice therapeutic range in your animal studies. Whether one can extrapolate that to humans, it leaves me -- I don't know, interesting question.

CHAIRPERSON FINNEGAN: Dr. Tuan, did you want to add anything?

DR. TUAN: Sure, just around that one point. Just along that same direction, a question that I think ought to be addressed is also that different cells respond to BMPs in the cell types and therefore, the different tissues respond to BMP with a different type of dose response, generally, in a nanogram for mil range or lower even. So I'm just thinking with -- about a couple milligrams at the site and then about one percent out there in the circulations. I can't do the math that quickly but maybe it will be useful to give the panel some

information as to, if you have the data that is, what is the local concentration of BMP at various tissue sites as a function of time, what the concentration may be and perhaps that may address some of the concerns of the panel.

DR. RIEDEL: This is Gerard Riedel speaking again. This is a topic which I started to address in my summary this morning. Dr. Tuan is correct in terms of the exposure that comes from the -- to the body from BMP implantation. And that is that we've observed in several animal models that approximately one-tenth of one percent of the BMP that's implanted at a local site becomes systemically available and is detected in the circulation.

This predicts a very low systemic exposure. But to address the issue that Dr. Tuan raised, that is that BMP has effects on different cell types, we administered BMP-2 protein in buffer by an intravenous administration to these animals and we did so with doses of BMP that were thousands of time higher on a per kilogram body weight basis than what was anticipated to be the human exposure as a result

of implantation of BMP-2 and the results that we found were uniform and they were striking in their uniformity.

We saw no effects. Now we know that there are cells that could respond, but we saw no effects and when we explored that further by looking at the pharmokinetics and the bio-distribution of BMP-2 in these animal models, we found that BMP-2 was very rapidly cleared from the circulation, principally by the liver and that it was rapidly degraded by the liver and cleared through the kidney and excreted in the urine within 24 hours and that's the explanation we think will --

DR. DOULL: Yeah, I think that's an important point. In order to define exposure, you need to talk about not only the dose but also the time and your kinetic studies have clearly shown that in 16 minutes it's gone in a rat and it's even less in a monkey. So in a human it's probably even less than that. So if you're defining exposure correctly in terms of both dose and time, then you're exposure is indeed, trivial.

CHAIRPERSON FINNEGAN: If I could -- go ahead. Microphone, microphone.

DR. TUAN: This might also address some concerns of another panelist and that is have you looked at the same thing in a pregnant animal and how much of the BMP that's administered to the pregnant mother is found in the fetus as a function of time, the pregnancy period?

DR. RIEDEL: I think it's very important for the panel, we'll keep the issue of the protein versus an antibody to the protein. We try and keep those as separate issues. We have only administered unlabeled BMP-2 protein in our reproductive toxicity studies but we did administer that protein over the duration that was described by Dr. Miller in his slides per the ICH guidelines for performing reproductive toxicity studies both before and during the early portions of gestation.

And in those cases, at exposure levels, again, that were calculated to be many times greater, more than a thousand fold greater than the anticipated exposure in humans. We saw no observations on any of

the parameters that were evaluated.

CHAIRPERSON FINNEGAN: Dr. Diamond, the floor is yours.

DR. DIAMOND: I have a few questions but can you just clarify for me something that I think I just heard but I'm not certain. You put in a total of five milligrams at a concentration of one and a half milligrams per mil; is that correct, into the sponge?

DR. RIEDEL: I'll be happy to clarify.

DR. DIAMOND: But it's not --

DR. RIEDEL: It's not quite correct, Dr. Diamond.

DR. DIAMOND: Okay.

DR. RIEDEL: Depending upon the volume of the sponge, we soak the sponge with a solution of BMP that contains one and a half milligrams of BMP-2 per milliliter of that solution. The reason why I can't give you a straightforward answer is that the total volume of solution that we use depends upon the size of the sponge.

DR. DIAMOND: But are you suggesting that if you use it at 1.5 milligrams per mil it doesn't

matter if the total amount of protein you give is 10 milligrams or five milligrams in that reasonably little space?

DR. RIEDEL: What we have advised surgeons and in all of our animal models was to fill the space with the volume of the wetted absorbable collagen sponge and not to over-pack it. And so, yes, in small defects that required small volumes of the wetted absorbable collagen sponge, the concentration of the applied BMP was the same but the total dose was different. So for small defects, they got a smaller total dose. Large defects in our animal studies got a larger total dose and what we found correlated with optimal therapeutic efficacy was the concentration of BMP that was applied to the sponge. That's the empirical observation.

DR. DIAMOND: I guess that's a little surprising, I think, but so I guess I had a question that was raised previously about are there studies with liver dysfunction? Is there limitations on who can receive this?

DR. RIEDEL: From a pre-clinical

perspective we have not looked at the pharmacokinetics nor the bio-distribution of BMP-2 in a liver impairment model and any animal model.

DR. DIAMOND: And do you know if the pancreatic tumor was receptor positive, the one that developed in the individual who got the --

DR. LIPSCOMB: They were negative.

DR. DIAMOND: And can I ask -- the patient.

DR. LIPSCOMB: Wait a minute, wait. You're talking about whether they were positive antibodies?

DR. DIAMOND: No.

DR. LIPSCOMB: Okay, I'm sorry.

DR. RIEDEL: Just to clarify the question, I think you were asking whether or not the patient in the clinical study who had a pancreatic tumor was positive for receptors for BMP-2.

DR. DIAMOND: Right.

DR. RIEDEL: Well, the patient is still alive about 13 months after diagnosis. We don't have any materials to assess.

DR. DIAMOND: I see, okay. That's a fair answer, a good answer even.

Can I ask some questions about the antibody studies? I guess it begins with were the studies in animals with the serum diluted one to 50 when I don't know, 30 percent of the dogs or whatever got -- or monkeys got antibody or was there different dilutions in the animals where there seemed to be more antibody?

DR. RIEDEL: I think it's appropriate to call one of my colleagues to the podium to address this answer.

DR. RUP: Bonnie Rup, Wyeth-Genetics Institute. So the question is --

DR. DIAMOND: Were the dilutions of serum the same in the humans and in the animal studies?

DR. RUP: They're basically the same starting dilutions --

DR. DIAMOND: So what --

DR. RUP: -- and we diluted out in order to get to a titer.

DR. DIAMOND: Why did you start at a one

to 50 dilution? I mean --

DR. RUP: Yeah, it's our experience that generally below that concentration one often sees very high background readings that gives you something that could be more variability in the background of your baseline which could be attributable to antibodies, perhaps. It could be interpreted as being attributable to antibodies but it's more likely to be due to just background high reactivity and especially in dogs. We had a lot of problems with high background.

DR. DIAMOND: So did you do any assays either in the animals or in human serum to look for neutralizing activity? I don't know what the most sensitive cell line to BMP-2 is. So I don't know which would be the most sensitive assay to look for neutralizing antibodies, but I assume that there are others here and elsewhere who know that. Did you look for --

DR. RUP: We have been talking to the FDA about developing a neutralizing antibody assay and we've made some attempts to start trying to look at a

cell line, the same cell line that's used as the bio-assay to determine potency of BMP-2, which obviously, is a logical choice. But there is -- that assay is in development. There has been some difficulty in trying to use serum on it, as you can expect. It's a cell line that produces alkaline phosphatase in response to BMP-2 stimulation and obviously, we'd be looking at a reduction in alkaline phosphatase production.

The serum itself also inhibits the cell line's alkaline phosphatase production. So we need to work on ways of reducing that as an issue.

DR. DIAMOND: Using your control, is your control, positive control, is it monoclonal?

DR. RUP: We have looked at -- we have a few antibodies that were generated as reagent antibodies, both monoclonal and polyclonal antibodies and those, obviously, we can test in a purified fashion, and we haven't seen any evidence that those are neutralizing.

DR. DIAMOND: But do you have -- can you calculate based on those how many micrograms per mil of antibody you have in the serum?

DR. RUP: Well, we've avoided trying to do anything like that because, as you know, antibody potency is really a function of both concentration and affinity. And there -- yeah, and so on, so we feel like reporting out nanograms per mil would be misleading because obviously, if you test it against a high affinity antibody, you get low numbers and if you test it against a low affinity antibody, you get high numbers and we just feel like that would be misleading and, you know, obviously, it's just relative to what you use to begin with, so we've never tried to do that.

DR. DIAMOND: I guess my concern is with the antibody testing that as you know, an ELISA depends how much antigen you put on the plate, what your starting dilution is, if you don't reduce the IgM antibodies and there are lots of IgM antibodies, you may not see the IgG antibodies that are present in the serum. And it's I guess a very artificial assay until it is validated with a gold standard of a biologic assay because do you know what kind of titer you would call at this point a clinically significant titer?

DR. RUP: Well, that's always a difficult thing to do because the intention of the assay was just to set up something that was very sensitive and would be able to give us a very reproducible assay during the duration of a long study. And so one always goes in with the intention of just developing a sensitive assay and you really don't know whether your assay is sensitive enough to pick up clinically relevant antibodies until you get clinically relevant responses.

DR. DIAMOND: Have antibodies been given to gestating animals or have gestating animals been immunized?

DR. RUP: No.

DR. DIAMOND: And I guess I have another question that will reveal what I don't know. This pregnancy registry certainly sounds like an appealing idea but how many pregnancies would you have to see to have a degree of fetal loss or teratogenicity that is important and how many child bearing -- women of child bearing age a year come to this kind of procedure. So over the five years we were told is realistic, are

numbers, the kinds of numbers that will give meaningful information going to be available?

And the answer may be clearly yes or I just don't know this.

DR. LIPSCOMB: Well, on that particular question I did try to run the numbers to see, you know, what you could come up with just based on the demographics of patients that were in our clinical trials and then taking some information that's available in the literature about how often do women get pregnant during the course of a year and I came up with this calculation.

DR. DIAMOND: Once.

DR. LIPSCOMB: As a whole. Not in Tennessee.

(Laughter)

DR. LIPSCOMB: But anyway, if you look at the slide here that's on the screen, for every 10,000 patients a year that would receive treatment, and I'm talking about all patients, not just women, based on our demographics from our clinical trials, about 5,000 of them will be women. And then if you look at the

age distributions that are in our study, then about half of those or about 2500 of them would be women of child bearing age.

And then this where the statistic comes in, I think we received out of a document that came from the FDA, in which this 11 percent of women of child bearing age in the general population would maybe become pregnant during the course of a year. So you multiply 11 percent times 2500 and you get down to a factor of about 275 women a year -- 275 women during the course of a year out of 10,000 people treated, would get pregnant in our patient population.

Then if you look at our antibody rate that we had in our clinical trial and you multiply that, you know, roughly -- surely less than five but the numbers calculate out to about two per year out of 10,000 people treated may be positive for antibodies they get pregnant. So you can see the number is pretty small, and even if you put safety factors, let's say -- well, not a factor of five. Let's get you up to 10.

And at the bottom of that slide, the

population rate, this would be -- what would be the adverse event that you would expect in the general population, whatever, the birth defect or whatever you would be looking for, if it occurs at one percent or three percent or 10 percent, and if you look at a relative risk of two, which would be the doubling of the rate versus the control, then you'd need those numbers that are underneath that patient.

So if it's one percent, you'd need 2,000 patients or 700 patients for three percent. So you can see by the numbers generated in the population and then what it would take in a registry, then to do anything statistically meaningful, it's kind of a hard thing for me to come to, you know, grips with when you start talking about a registry. And this also, too, takes into account a situation where you're just taking -- assuming that women are going to get pregnant. That doesn't take into account that, you know, women that have had back surgery which will probably lower that number some and it's also probably -- you know, you might tell them not to get pregnant, you know, for some period of time, so that will reduce

it even more.

In our clinical trial, only about 1.5 percent of the people got pregnant. I know there was a question, you said, you know, when did these people get pregnant and everybody got pregnant in the study after 16 weeks except one. There was one, I think, at about eight weeks and that pregnancy went to a normal delivery. So the other thing, too, that was mentioned, I think, in Dr. Miller's talk this morning when he was going through the registry concept, tell me when to be quiet, but he gave several reasons why you might want to do a registry, I think at the end of this talk and it seems like to me some of those points that you made wouldn't fit our particular situation which was, say maybe a registry wasn't appropriate here.

So that's -- I hope that answers your question.

DR. DIAMOND: I guess it seems to me though that the numbers of patients who are going to accrue over five years and the number of anticipated pregnancies is probably at the low end of where you're

going to be able to detect teratogenicity for sure and even fetal loss and so I think that makes it all the more important to look in animal models to see whether these antibodies have a potential negative effect on pregnancy outcomes.

DR. RIEDEL: I just wanted to add one piece of information. We have looked very hard in making monoclonal antibodies to recombinant human BMP-2 to make an antibody that would neutralize the activity of the protein and we've tried for now eight, nine years and we have yet to make a neutralizing monoclonal antibody against this protein. So we do have some technical issues that we have to address as we work with FDA on this matter.

CHAIRPERSON FINNEGAN: Are you comfortable -- you're comfortable with the answers? Dr. Hanley, questions?

DR. HANLEY: We have one question and that relates to one of those letters that was read earlier about putting the BMP adjacent to the nerve for a posterior approach. It doesn't relate to the indication being sought for here but any comments from

people on that?

DR. BODEN: Obviously, the risks and complications of the device are that of the surgery, the insertion of the cage and what's inside the cage, and this specific application before the panel today is through an anterior approach, either an open or a laparoscopic and to talk about safety issues that are related to a different surgical approach seems to me to be outside the scope of what we ought to be focusing on today.

CHAIRPERSON FINNEGAN: Actually, I'll take a little bit of exception to that because you know that in the skilled hands of the people who did your trial, that was placed where it was supposed to be placed, but if it goes out into the free market it's going to be probably placed close to nerve roots and I think that's a really valid question.

DR. BODEN: Okay. We can go into it in a little bit more detail then. Why don't we go to slide 36? The issue with the study that's been raised was a study where the cage was inserted through the posterior aspect of the spine. Why don't we go

forward one slide actually?

And so there was no longer a barrier, in fact, between the cage and the InFUSE™ bone graft and the neuro elements. One of the other things that happens when you insert cages from behind is, in fact, that you have roughened surfaces of bone. You can have hematoma, sometimes hemostatic agents are put in place. As we see from the anterior insertion of the cage, it is in fact, not uncommon to see bone formation in front of the cage from the direction of the surgical approach.

Somebody referred to it earlier as a sentinel sign. I think it might have been Dr. Kostuik and in fact, that's a very positive thing. Why don't we move forward another slide? So the notion that there would be bone forming in front of the cage, and this is, of course, a patient from the application we're discussing today which is from the front of the spine, the notion that you would have a bump or bone in front of the spine, otherwise known as the sentinel sign is, in fact, a normal and a desirable finding.

However -- why don't you back up one for

a second -- if that sentinel sign occur -- if the insertion of the cage is through the canal and that sentinel sign, if you will, is a reverse sentinel sign, and occurs posteriorly, then that can potentially encroach into an area where there are nerves. Forward.

So I would say that it's not at all an unexpected finding. It s something that, in fact, with posterior lumbar interbody fusion with the same cage filled with autogenous bone graft we see variable amounts of bone formation and the patients in that study were analyzed in great detail looking at how often that occurred and it was with an intermediate degree of frequency and to differing degrees or the size of the bump, just like we would expect from that anterior approach, but I think the most important thing in that trial was that the presence or absence of that little bony bulge did not correspond with any clinically measurable differences between the groups.

So it was a radiographic observation that I would say is not at all unexpected based on our experience from putting them in from the front of the

cage and it is something that, you know, when you look at the groups as a whole, groups of patients that had, you know, a little bit of bone versus no bone, there was really not a clinically detectable difference in their outcome. Does that --

DR. LARNTZ: Could I follow up just from that statement? Did you actually do a statistical analysis of that?

DR. BODEN: No.

DR. LARNTZ: Okay, that's all I wanted to say.

DR. BODEN: Does that answer the question, Dr. Hanley?

CHAIRPERSON FINNEGAN: Just one addendum to that; was the PLIF -- I don't think you were part of it. Was the Sofamor Danek PLIF study with the cage not stopped because there were some problems?

DR. BODEN: Yeah, the trial was put on hold and that was actually a somewhat controversial decision which I can take some personal responsibility for because I was not one of the participating surgeons in that trial and the surgeon group met and

analyzed this when it first became apparent that people were observing it and actually felt very strongly about continuing the trial.

I, as a consultant, wanted to actually watch these patients longer and make absolutely certain that this was not going to be of clinical consequence and made the recommendation to Medtronic Sofamor Danek that they consider holding the study until there could be more follow-up and a better determination of the extent of what this observation meant.

And it was after that deliberation that the study was put on hold merely to follow these patients.

DR. DIAMOND: Can I ask something following up on this?

CHAIRPERSON FINNEGAN: Yes.

DR. DIAMOND: Didn't we hear in a letter that there was one patient who had bony ingrowth into the spinal canal?

CHAIRPERSON FINNEGAN: I think Dr. -- is Dr. McCullough still here?

A VOICE: No.

CHAIRPERSON FINNEGAN: He left but I think Dr. McCullough's presentation had from using the material posterially with a --

DR. DIAMOND: That was post --

CHAIRPERSON FINNEGAN: It was in a letter.

DR. DIAMOND: Right.

CHAIRPERSON FINNEGAN: Yes.

DR. WITTEN: Yeah, I just want to mention that to the extent that these things -- you know, these other studies relate to the effectiveness of this indication, then I think asking questions is appropriate but to the extent that they're just about some other use, we really want to focus the discussion here on the particular indications sought by the sponsor.

CHAIRPERSON FINNEGAN: Understood, understood, but I think there is some relative safety as far as leaving some space. Yes, Dr. Kostuik, did you want to add to that? Yes, Dr. Miller. He's cleaning his glasses.

DR. MILLER: While he's cleaning his

glasses, perhaps Dr. Diamond and the group here could address an issue I've been fumbling with. We have three patients who are positive on antibodies; one an experimental, one in the control and another experimental that was, in fact, positive before they -- in the pre-op stage. Now, does this mean really we have a small segment of the population that is carrying these antibodies not associated at all with your giving BMP-2.

If you took 500 women, pregnant women and screened them, how many of them would have that antibody?

CHAIRPERSON FINNEGAN: Well, I think that relates to Dr. -- to Barbara's question, too, so hang on a second and we'll get around there. Gene.

DR. SIEGAL: I'd like to go back to the pancreas because I did not understand the answer. You said the patient was still alive. Certainly the diagnosis was made by either open biopsy, by fine needle aspiration or perhaps by radiologically guided brushing. Any one of those should give you enough cells to seek the answer that was requested.

DR. LIPSCOMB: They performed surgery on this gentleman.

DR. SIEGAL: So you do have tissue.

DR. LIPSCOMB: Yes. I don't think the receptor has been looked at though.

DR. SIEGAL: Okay. So let me then go back and ask that question I asked before which is two cell lines appeared to show increased mitogenesis and one patient developed pancreatic cancer, the first two were pancreatic cell lines. How do you interpret that cohort of data?

DR. BODEN: When we looked at the expected frequency of tumors in the population of this size and age and demographics, it turns out that the number of tumors is actually less than what you would expect in the population. The issue that the -- you know, that one of the tumors happened to be pancreas, I think at this point it would be hard to make any statistical case that would be more than just coincidence.

The other thing is --

DR. SIEGAL: There was two, were there not, two cell lines, one?

DR. BODEN: No, no, in the cell lines.

DR. SIEGAL: Two cell lines, one patient.

DR. BODEN: There were two cell lines. There were also pancreatic cell lines that did not have that response and also when you look at tissues from tumors which Dr. Riedel presented earlier in none of the transformed tumor cell lines, so none of the live tissue that came out of patients with tumors was it ever observed that there was that increase in division.

DR. SIEGAL: Okay, thank you. Now, I want to go back to my question about whether or not there were pathologists involved in any of these studies.

DR. RIEDEL: Can I just ask one clarification?

DR. SIEGAL: Yes, please.

DR. RIEDEL: Are you referring to the animal studies that looked at spine fusion or the animal studies that looked at the safety of the implanted product?

DR. SIEGAL: I guess I would ask in any studies were there board certified veterinary or human

pathologists involved?

DR. RIEDEL: For the animal safety studies the implant safety toxicology studies were conducted at a contractor, Clinical Trials Bioresearch in Centerville -- in Canada. On staff were board certified pathologists and veterinary surgeons. To the best of my recollection, I can't remember at this moment and will have to get back to you on whether the histologist was a board certified veterinary histologist but I believe he was.

DR. SIEGAL: And so you don't know either whether they have any expertise in bone pathology.

DR. RIEDEL: Oh, no, I'm sorry, I should follow up with that point. We did specifically ask for people with specific expertise in bone biology to assess the histological samples from these studies.

DR. LIPSCOMB: We also have here Dr. Jeffrey Toth, who has done histological reports as well on samples.

DR. TOTH: Yes, I'm Jeffrey Toth. I'm an associate professor of orthopedic surgery at the Medical College of Wisconsin, also direct the

biomaterials laboratory for orthopedic surgery. I have no financial interest in the company or product being reviewed here today nor any other company or product.

I am not a pathologist. I have done work over the last 10 years that has involved bone histology as a method of analysis for biomaterials and bone implants. I have about 25 publications and peer review publications and book chapters in that area especially dealing with spinal implants.

There were four pre-clinical studies that Dr. Boden talked about his morning. Our laboratory actually did histology on two of those, so I don't know exactly which ones you're referring to. If I could have slide number 13, please. Our laboratory actually produced the histology for the --

DR. SIEGAL: I don't wish to in any way impugn your reputation but I just want to make sure you said you're not a pathologist.

DR. TOTH: I am not a pathologist.

DR. SIEGAL: Thank you.

DR. RIEDEL: Dr. Siegal, my colleague just

corrected me and I should correct for the record, the folks that did the work for us at Clinical Trial were not boarded histologists. They were boarded veterinary pathologists.

DR. SIEGAL: In the human studies, were there any human pathologists involved?

DR. RIEDEL: Well, Dr. Toth did the analysis in the human explants.

DR. SIEGAL: Okay, thank you. Then the next question, I guess, out of order if you will was, would there then not be value in performing a study comparing the radiology to the pathology in animals with appropriate expertise in pathology and radiology?

DR. ZDEBLICK: Good afternoon, my name is Tom Zdeblick. I'm an orthopedic surgeon at the University of Wisconsin. I do have a financial interest. I'm the inventor of the LT-cage and I have patents on the LT-cage and one of the four studies that were quoted this morning was the original one that I did with goats using a different cage, titanium cage, using BMP-2 and that was performed at our School of Veterinary Medicine at the University of Wisconsin.

And that correlated the radiographs and the pathology read by a certified veterinary pathologist, two of the mechanical results that we found in that study.

And there was very good correlation between what we saw in histology, the radiograph and the mechanical performance.

DR. SIEGAL: Thank you. The last question I have had to do with whether you consider preloading the cage with already hydrated BMP-2 in the sponge, to minimize the amount of handling required at the time of surgery.

DR. RIEDEL: Yes, Dr. Siegal, we did consider that but there are significant technical obstacles to generating, to manufacturing such a preloaded material. We have chosen to go with aseptic manufacture of the protein in order to preserve the integrity of the protein and avoid any problems associated with damage to the protein due to terminal sterilization of the product.

The collagen sponge is terminally sterilized with ethylene oxide treatment. We wanted to avoid the potential damage to the protein

associated with that terminal sterilization. Consequently, we have performed validation studies using radiolabeled BMP-2 to validate that the method that we use for instructing the surgeons to apply the protein results in a uniform application of protein across the entire volume of the wetted sponge and that information has been provided to the agency in the application.

DR. SIEGAL: Thank you very much.

CHAIRPERSON FINNEGAN: Dr. Kirkpatrick.

DR. KIRKPATRICK: I think a couple of my questions can be dispensed with fairly quickly but first with a yes or no question with regard to my question raised during the presentation. Have you identified the specific reason that the patients in the control group developed an antibody to the bovine collagen? Was it because the surgeon used a hemostatic agent during the surgery?

DR. BODEN: There's no way to know that for sure, but certainly people are exposed to bovine products in many aspects of life in addition during surgery, and so any gelatin-based product of some

kind, you know, sutures and things.

DR. KIRKPATRICK: So as a yes or no question, it's no, you don't know?

DR. BODEN: We have no way of confirming that.

DR. KIRKPATRICK: Right, that's all I wanted to make sure.

DR. BODEN: Nc.

DR. KIRKPATRICK: Thanks. Sorry, Scott, but there's a lot of people trying to catch planes tonight. With regard to the radiographic data beyond 24 months and the clinical data beyond 24 months, can you just give me again as short an answer as possible, did you see the deterioration continue that you demonstrated between 12 and 24?

DR. BODEN: No.

DR. KIRKPATRICK: In other words, we can assume that even though there would be a smaller number of patients beyond 24 months, that we would find percentage of fusions approximating the ones that you saw at 24, no more than a five or 10 percent --

DR. BODEN: Understand that the 48-month

follow-up is really limited to the pilot study which had 11 investigational patients and three autogenous bone.

DR. KIRKPATRICK: Would you not also have a number at 36 however?

DR. BODEN: It wasn't part of that study.

DR. KIRKPATRICK: So once the 24 months was up those patients are no longer studied?

DR. BODEN: Are you talking in the pivot trial or the clinical?

DR. LIPSCOMB: I'm talking about the clinical trial between the open -- the two open groups. You didn't do them all in the first month of the trial.

DR. BODEN: No, I mean, there --

DR. KIRKPATRICK: So I know you've got patients beyond 24 months that might be at 36. I'm wondering since you showed in your data that you deteriorated I think it was like four percent between 12 and 24, did you continue to see that between 24 and 36 even though you're probably down to what, 50, 75 patients at that time?

DR. BODEN: The best long term follow-up going out to four years is in eight of the 14 patients from the pilot trial which is essentially the same protocol. And in there, there was five investigational and three control and at the 48-month follow-up five out of five in the investigational were still deemed as fused radiographically and the same two out of the three of the control were rated fused. So there was no change in the primary outcome variable which was radiographic fusion at 48 months.

What happens to change in the overall success rate that you're observing is not a change in the radiographic or CT determined fusion success. It's patients that over time may, with their surgeons, decide to have another operation or may require another operation for an adjacent problem. So the definition of success was very strict in that if anything occurred.

And so what you're seeing with that quote, unquote "deterioration", is not really a change in the hard core result of bridging bone but rather that those other criteria that go into the more clinical

fusion rate.

DR. KIRKPATRICK: What I saw in at least one of your case reports of a failure was that between 12 months they were deemed a fusion and at 24 they were a failure because of a pseudoarthrosis, okay, specifically in your case example. So what I'm asking is, did that happen after 24 months.

DR. BODEN: That was because of a second surgery, not because of a radiographic change in reading. That patient was --

DR. KIRKPATRICK: The clinical report that I saw said he had a pseudoarthrosis, period, okay. A pseudoarthrosis is a failure even if it took an operation to discover it.

DR. LIPSCOMB: That was the reason for the second surgery that was filled out on the adverse event form. That's why the second surgery was performed. It was a diagnostic reason for why a second surgery. We take a conservative approach there. Regardless of what the radiograph show on the fusion criteria, if a patient is still having pain or whatever and the physician says that I had a suspected

pseudoarthrosis here, then they -- and if they do a second surgery, they may put pedicle screws on the other side, we count that as a fusion failure, just because the surgeon called it a suspected or a possible pseudoarthrosis, even though it may not jive at all with the radiographs.

DR. KIRKPATRICK: I'm sorry, I didn't memorize the number of the patient so we could discuss it specifically. However, the report I read did not say possible pseudoarthrosis. It says he was reoperated on because it was a pseudoarthrosis. If that data is not correct, I'd like to know. If it was, I'd like to know if you followed the patients that are now beyond 24 months and found if you have any more.

DR. LIPSCOMB: The protocol for the pivotal trials specify that patients are seen after 24 months and then bi-annually which means every other year, thereafter until every person in the study has gotten two years. That's the criteria, so there is no 36-month visit for patients to come back in according to the schedule. Forty-eight would be the next one

provided that everybody didn't get to 24 in the meantime.

I am aware, I think there's been a couple of second surgeries after 24 months, though.

DR. KIRKPATRICK: If you had said that in the beginning, my question would have stopped. If I knew you weren't looking at anybody from 24 until 48, that was -- you can't answer my question. I think you've already answered my question on the liver. You don't know, correct?

DR. LIPSCOMB: That's right.

DR. KIRKPATRICK: I think in the interest of time, the expression of the BMP in a normal is probably not worth discussing. I would like, however, to know your specific recommendations as far as my other question on the off-label use, which is, in light of the history of the pedicle screw issue and the off-label use there and resulting litigation, how would you guard against off-label use of this product especially with rhBMP-2?

DR. LIPSCOMB: Well, you mentioned the pedicle screw situation. That is -- that's an

interesting concept because when we, as a company, were dealing with that issue, and in discussing labeling throughout the years with FDA, when we started talking about a warning or a precaution or some statement like that about, "Don't use a screw in the pedicle", it came back that if you tell somebody not to use a screw in the pedicle, that's in essence an indication.

So a contra-indication or a warning would be an indication. So we couldn't basically do that. I think we could propose labeling or would propose labeling. We'll discuss it more with FDA when we're discussing the final labeling, but statements could be made or -- along the fact that safety and effectiveness of InFUSE™ bone graft and other spinal applications has not been established.

DR. KIRKPATRICK: Thank you.

CHAIRPERSON FINNEGAN: Thank you, Dr. Kirkpatrick. All right, just a couple of short questions. The question of elution within the titanium cage, has that been looked at and a second part of that question is, do you know if there's any

affinity for titanium ions and the BMP?

DR. RIEDEL: Neither Medtronic Sofamor Danek nor we have looked at the bio -- the clearance of BMP implanted in a titanium cage. We have, however, looked at several animal models that have used different geometries of the implanted rhBMP-2 ACS and in general the clearance from the implantation site follows the same time course and the same general pharmokinetics from the site.

With respect to your second question about interaction with titanium ions, we have done no studies to look at interactions with any metal ions and the BMP-2.

CHAIRPERSON FINNEGAN: The next question is, any idea why the ones that failed, failed? I mean, it's a pretty simple standard --

DR. LIPSCOMB: It depends on what you mean by fail. If you're talking about overall success, failure, why that rate is what it is?

CHAIRPERSON FINNEGAN: Actually, did not fuse. The other back pain patient population problem we're not that interested in but didn't fuse.

DR. BODEN: Actually, there's very few, if any, that did not fuse based on using the CT criteria, bridging trabecular bone. The ones that are -- and this is a bit of a confusion because of the way the protocol is defined and the way it's presented, a radiographic failure technically could be somebody who is fused but had another operation because they had persistent pain or had adjacent segment degeneration.

And that would be shown as a radiographic failure. If you separate out the radiographic -- the definition of radiographic success as bridging trabecular bone, I think Dr. Genant will say that every patient met that criteria.

CHAIRPERSON FINNEGAN: No, but at least I know there are two women over 50 who had migration of their cage and one of them very definitely. Those x-rays and CT scan I could see --

DR. BODEN: Yeah, that's -- I'm sorry, that's a completely different situation. Those were early failures because of technical problems with the cage insertion irrespective of whether the cage is filled with autogenous bone graft or infused bone

graft. That's a cage technique insertion problem that surgeon technical irregularity.

CHAIRPERSON FINNEGAN: Because one of them was not approached surgically again, but still did not fuse, so I would assume that the material is still there and the BMP is still in the cage.

DR. BODEN: The BMP is going to be gone from the cage presumably within in 14 days. And there are a number of different animal studies and a variety of different venues to support that, as well as somebody asked earlier about the -- or it's one of the questions about the collagen sponge. That's going to be resorbed in four to six weeks most likely, depending on the animal model.

So I think if a cage was sticking out front what you have is a situation where you don't have the adjacent bone in order to develop blood supply and have a continuous or connecting bone. So that particular cage in a sense would be an isolation, but if there's a case where --

CHAIRPERSON FINNEGAN: You have soft tissue there.

DR. BODEN: Huh?

CHAIRPERSON FINNEGAN: You have soft tissue around it. Anyway, never mind. You obviously haven't looked at it. My last question, I think, for your vice president is, when I looked at the materials that you sent it looked like these were all packaged together, that is the cage, the BMP hydrated and there was one picture that had sort of what this was supposed to look like. And I guess my question is, if you have different sized cages, do you have different sizes of the sponge but the same -- this is like somebody else's question -- but the same amount of BMP?

DR. LIPSCOMB: Yes. The key point as Dr. Riedel said is the concentration of 1.5 milligrams per milliliter and depending on the size of the cage, it would take different sizes of vials of BMP.

CHAIRPERSON FINNEGAN: So both the sponge size and the vial size differ.

DR. LIPSCOMB: Right, because it would be the inner lumen. It would be the inner lumen of the cage that would dictate what size sponge to put in.

CHAIRPERSON FINNEGAN: So that goes back to my question about packaging. So then for each size cage are you going to have an associated size vial of the BMP and associated size of the sponge?

DR. LIPSCOMB: Well, the BMP kits will be sold with a certain size vial with the sponge inside the kit. The cage will be sold separately or will be, you know, not packaged with that.

DR. RIEDEL: There is a volume to volume.

CHAIRPERSON FINNEGAN: Right, but if your cage volume is different then you have to match the cage volume to the sponge size and to the volume of your -- okay, and the consumer is going to know this by -- so I guess two questions then. The InFUSE™ is going to be sold as a separate unit. It's not sold with the cage.

DR. LIPSCOMB: That is the plan, yes.

CHAIRPERSON FINNEGAN: Okay, and so then how is the consumer to know which size of InFUSE™ goes with which size of cage and how do you control that?

DR. LIPSCOMB: It would be in the

labeling.

CHAIRPERSON FINNEGAN: All right, but then the surgeon could, in fact, use more or less at his or her discretion because they could just buy a different size package.

DR. LIPSCOMB: Well, the inside of the cage would dictate what size kit would be required to fill the cage. I guess I'n not understanding the question but --

CHAIRPERSON FINNEGAN: Actually, I think you're not understanding the creativity of orthopedic surgeons, that's my concern.

(Laughter)

CHAIRPERSON FINNEGAN: You answered the question. Dr. Naidu?

DR. NAIDU: Yes, I have a couple of short questions. The question about excess bone formation, you guys talk about surgical technique. Dr. Boden goes into in detail but just looking at your manual, nowhere do you describe the preservation of the posterior annulus, just be careful about not -- you know, you talk about not perforating through, but is

that going to be addressed in a manual in more detail as to how not to place it too close to the nerve roots or -- I mean, as far as the technique, the surgical technique?

DR. ZDEBLICK: The surgeon technique manual is pretty specific about templating for size and the templating takes into account the area of the disc space and how far away from the posterior longitude and the ligament you need to stay and then second, when you're preparing the channels for the cages with the reamer, they're depth specific and depth stop will keep you in that range so that you inadvertently don't go too far posterior.

So at several steps in the technique manual it addresses that concern.

DR. NAIDU: Okay, thank you. And the second question is, the size ranges of your cages, what were the size ranges, small to the largest, the diameter of the cages?

DR. MATHEWS: Yeah, the cages range from 14, they go to 16, 18 and 20 millimeters.

DR. NAIDU: So 14 is your smallest

diameter?

DR. MATHEWS: Yes, and they have different lengths from 20 to 26 millimeters in length.

DR. NAIDU: Okay, now, so when you're seeing these -- this bone formation at 12 months on CT scans, what we get are a couple of reconstructions at 12 months and 24 months and you're saying that the dowel of bone that forms between the two segments is, at best 14 millimeters thick -- I mean, I'm sorry, at best 22 millimeters thick and if you use the smallest cage it's about 14 millimeters thick. Is that what those radiographic data mean?

DR. BODEN: Yeah.

CHAIRPERSON FINNEGAN: Scott, you need to state your name for the record, so the transcript shows it.

DR. BODEN: I'm sorry, Scott Boden. What -- the early fusion tends to be through the cage. That's the way the device works whether you're using autogenous bone graft or InFUSE™. So this is a question that really is, in a sense, independent of what is causing bone to form. However, what you see

over time is bone forming around the cages or what is secondary bridging across the interspace. It can be in front of the cage or the sentinel sign, that we discussed earlier. We showed examples of it going around the sides of the cages.

We see a clear trend that in the case of InFUSE™, which seems to have more reliable bone form earlier based on measuring units on CT scans, that we tend to see more reliably this bone around the cage. So, if anything, I would say that you get additional bone sooner and more reliably in the InFUSE™ cases but that's not a statistical observation. It was not an official endpoint. It's a empiric observation, but it ultimately gets to the same endpoint in appearance if you had used autogenous bone graft, but it appears to get there quicker with some of those additional areas and zones of bone formation.

DR. NAIDU: Okay, thank you. And the next question that I have is more directed towards our experts, Dr. Kostuik mainly. Dr. Kostuik, you talk about flexion/extension views not being too reliable with the advent of this posterior instrumentation

world that we're in today. Would you say that the flexion/extension criteria that the sponsor has established such as less than three millimeters of translation and less than five degrees of angulation, with the use of these cages is a valid radiographic criteria since -- if you could expound on that.

DR. KOSTUIK: I would say that they are not valid. There's too much variation in how the patient is positioned, how the x-ray is taken, slight location of patient during taking the lateral view, but the most particular reason for my saying that is that these implants provide very significant rigidity at least within the first few months, and it's certainly been, I think, well-shown and a long-term practice with other forms of anterior cages that flexion/extension x-rays are not statistically valid in assessing motion.

DR. NAIDU: Thank you. Those are all the questions I have.

CHAIRPERSON FINNEGAN: Thank you. Dr. Boyan?

DR. BOYAN: Well, I don't really have a

question. I just wanted to state again -- maybe my question is really for Integra. On the -- in the Helistat™ sponge, you clearly have had 20 years experience with that clinically, have you found that patients have become sensitized to the type I collagen in the sponge or that particular type of type I collagen where if they've had repeated procedures, that they don't develop an immune response?

DR. O'GRADY: Good afternoon. I'm Judy O'Grady, Regulatory Affairs, Integra Life Sciences Corporation. We're the manufacturer of the absorbable collagen sponge which is also known as Helistat™, also known by other names.

Let me start off by saying that there is a 21-year history, as you mentioned, of this -- of approvals through FDA and marketing of the absorbable collagen sponge. In our experience in marketing this product as an implantable medical device, and also in numerous clinical trials and the clinical trials involve often repeated application and multiple applications of the collagen product, not necessarily the Helistat™ but we -- all our products are

manufactured from the same source of collagen and also undergo the same purification process.

To this date, in 21 years, both in marketing the product and in clinical trials, we have never seen any immunogenic response or allergic reaction to the product.

DR. BOYAN: Okay, thank you. And then not to cause a problem but, Dr. Riedel, I'm going to turn it over to you on the BMP side of things and the only reason why I do this is just to clear the air but BMP, you know, it revs a lot of things up and it does, in fact, rev up some times immune cells. They're there and it isn't a -- I mean, it's -- they're not unhappy but they're energized.

And so have you done -- in any of your animal studies have you looked at this specifically?

DR. RIEDEL: Other than performing a histological assessment at the site of implantation, we have not looked at specific immunological markers in any of our studies.

DR. BOYAN: Okay, thanks.

CHAIRPERSON FINNEGAN: Thank you. Dr.

Reddi.

DR. REDDI: Yes, my questions and issues are for the folks from Medtronic Sofamor Danek and their collaborators and Wyeth-Genetics Institute. As far as the tumorigenicity in which the FDA has specifically charged the panel to provide guidance to the FDA, I'd like to follow up with one of the experts from the sponsors. In addition to studying the effects of recombinant human BMP-2 on transformed cell lines from one of your grantees in Texas, has there been any direct long-term effects on either mice or rats to see whether there might be any in vivo tumorigenic actions, positive or negative?

DR. RIEDEL: I'll start just by summarizing the results that I presented this morning and that is that we conducted in canines and in rats a chronic toxicity study with endpoints at various time points to either six or 12 months of follow-up and did extensive histological assessment of the implantation site in those animal models.

Using local concentrations of BMP-2, they've greatly exceeded the therapeutic optimal

concentration, local concentration, for those specific species and in both of those animal models, we saw no evidence of any abnormal cellular events that would be suggestive of tumorigenicity in those models.

DR. REDDI: All right, I take it, it was mostly confined locally to an osseous environment.

DR. RIEDEL: In both instances, you are correct, Dr. Reddi. The implant resulted in a formation of an osseous environment at the site of implantation.

DR. REDDI: Yes. I was most impressed by your presentation and description of the effects or recombinant human BMP-2 on the femoral onlay model. Now, in your extensive pre-clinical studies at Medtronic, either Scott Boden or some of the other three centers, has there been an attempt to do the same experiment of placing such a device, InFUSE™ in the environment of the disc?

DR. RIEDEL: I'll start the answer by referencing a safety study that was done in a canine model in which the safety of BMP-2 on the absorbable collagen sponge was assessed when it was applied

directly to the dura of the spinal cord following an laminectomy procedure. This study was conducted as a GLP study in an academic laboratory and it was actually Dr. Hanley's lab that performed this study and the results of that study have been published and there were no significant findings in that study.

DR. REDDI: There is a lot of panel members at various times have asked already questions about the antibody and the transplacental passage and I had given you a heads up to tell me whether you have antibodies to the native recombinant BMP-2 and what happens if such antibodies are administered to rats or mice.

DR. RIEDEL: I'm going to defer to my colleague to address this question.

DR. RUP: I'm Bonnie Rup, Genetics Institute, Wyeth. You're referring to antibodies that were made as reagent antibodies? Yeah, the only antibodies that we were able to make by immunizing were actually against Ecoli-derived, onimeric (ph) BMP-2, or against peptides conjugated to immunogen proteins.

DR. REDDI: And when you administered -- did you administer to pregnant mice or rats and what effects did it have on the embryos?

DR. RUP: We never tried to administer them to animals. I can't tell you that we've tried to look to see whether they have neutralizing effects in cell-based bioassay and they don't seem to neutralize.

DR. REDDI: Yes, and it is also well-known, even the best antibodies made by Wyeth-Genetics Institute the recombinant BMP-2 cross-reacts with BMP-4. Would there be a concern that these antibodies in these patients might effect functions which are directed in the embryo or elsewhere by BMP-4 or do you think it would be a concern that we should address?

DR. RUP: I think that the antibodies that -- you know, the few antibodies that can be generated in humans, they might cross-react with BMP-4 since they're very homogenous.

DR. BOYAN: May I make a comment, Madam Chairman?

CHAIRPERSON FINNEGAN: You may.

DR. BOYAN: I think that we're all dancing

around about the antibodies and I'm going to take the risky thing of saying something out loud scientifically and hope that I'm right but it isn't easy to make an antibody to native recombinant BMP-2 and I think everybody needs to know it's not easy to make one and it isn't easy for humans to make one. This is a highly conserved common protein that we have in our bodies all the time.

Generating an antibody to it is not a small feat and that's why they've had to go through such extensive things to generate them to peptides and hook them onto stuff to get the antibodies made.

DR. RUP: And we definitely concur with that.

DR. DIAMOND: Can I just say one thing, though?

CHAIRPERSON FINNEGAN: Yeah.

DR. DIAMOND: I think that the experience with recombinant human proteins in people is that when you give it to enough people, you get antibodies.

DR. BOYAN: I agree.

DR. DIAMOND: And that we know this with

thrombopoietin, with erythropoietin, these are recombinant human proteins. They shouldn't be immunogenic and I think it really depends on having an assay that can look for an interference with biologic function and that's very important because, you know, very immunogenic, not very immunogenic, eventually it will be immunogenic.

DR. BOYAN: I agree. I didn't say it was impossible. I said it isn't easy.

CHAIRPERSON FINNEGAN: Dr. Lenchik (sic).

DR. REDDI: The last question I have for perhaps Dr. Boden or somebody else from Medtronic Sofamor is that since when you first put the cage with the InFUSE™ device, the cells which are going to see it are either the nucleus palposa (ph) cells and/or the annular cells, has there been some basic studies to find out the responsiveness of these cells at what you might call a therapeutic index concentrations? How do they respond?

CHAIRPERSON FINNEGAN: Don't all jump at once there?

DR. BODEN: Scott Boden. We have

histologically not observed any changes in the surrounding cartilage. As part of the procedure, obviously the cartilage is removed in order to create the crevice or the tunnel that the cage goes into. And the cells that really grow into the sponge, which is where the BMP is and if the BMP elutes into the adjacent bone because of circulation, tends to be more of an exchange with bone cells and marrow cells than the relatively acellular and quiescent intervertebral disc cells.

In most cases these discs are very degenerative and so the cellular activity is somewhat low. There are a number of in vitro studies looking at BMP-2 and others effects on disc chondrocytes and again, those are in vitro studies. There have not been any deleterious effects that I know of. In fact, many of them are thought to be beneficial and whether or not that would be possible with a single dose application, as in this case to make any difference I suspect probably not.

Most of those beneficial attempts at intervertebral disc cartilage therapeutics are more

with longer term exposures or gene therapy approaches.

DR. REDDI: Thank you.

CHAIRPERSON FINNEGAN: Dr. Lenchik?

DR. LENCHIK: I have a couple of questions, hopefully it will be brief. To get back to that question of posterior anatomical barrier that exists behind the cage, what do you do about patients that have annual tears or worse disc herniations? Is the labeling going to be such that this device is contra-indicated in those patients or how do you keep them from ossifying the spinal canal?

DR. BODEN: Scott Boden. I think that's a very appropriate question and, in fact, as you know and others know, the normal population has a very high frequency of annular tears. Some of them are microscopic, many of them are macroscopic. Patients can have defects in the annulus because they've had previous disectomy or current herniated discs.

We believe that all of that existed because this is a normal disc population and remember that in order to form bone at a distant site away from the implantation site, it requires not only the

elution of recombinant BMP-2 protein but it requires a matrix or a substrate in order which to form the new bone on. So in none of these hundreds of patients which inevitably, based on pathologic studies we know from the prevalence of annular fissures and tears was that an issue in the pilot clinical or in the pivotal clinical trials.

DR. LENCHIK: So there was not a single patient that formed bone posterior to the cage?

DR. BODEN: There was not a single patient -- Scott Boden again. There was not a single patient that formed bone posterior to the cage outside the confines of the disc case. Remember bone in the confines of the disc case, anterior, posterior, laterally to the cage is a normal finding that we see even with successful autograft fusions over time.

DR. LENCHIK: A second question, a repeat to what I asked earlier, what do you think the explanation is for why the number of patients fused by CT criteria were less at 24 months compared to 12 months? Were these initial false positives at 12 months and did you look at that group specifically to

see if there was any correlation with clinical symptoms in that small group?

DR. BODEN: Scott Boden again. That drop in the apparent fusion rate was all due to the second surgery criteria. Those were all people that had operations, for reasons as I stated earlier, that may have either been persistent pain, new pain, adjacent segment degeneration. So it was not a change in the radiographic reading or appearance or the grading of the CT scan.

So in a sense, in terms of positivity, false or otherwise, the numbers and the statistics that you're probably thinking of were radiographic fusion rate, include in it the requirement that there not have been a second surgery in order to be considered a fusion success as the study is currently defined. So the apparent drop in that percentage is because of some patients that are getting second surgeries.

DR. LENCHIK: I guess you confused me by that. So what you're saying is that actually the number of CTs that were fused was not less at 24

compared to 12?

DR. BODEN: That's correct.

DR. LENCHIK: The other question is also somewhat a repeat of what was asked earlier but I'm not sure I heard an adequate response. Was the radiographic assessment of fusion either by CT or plain films, was there any quantitation of that? I thought somewhere in the document I read that it was graded one through four and A through D, and if so, how much of it did you need before you called it fused, either on plain film or CT?

Was one trabecular bridging across sufficient or how much of it was required?

DR. BODEN: This is Scott Boden again. The grading system you're referring to was created in the pilot study as a means of assessing whether or not that type of quantitative analysis would be helpful or not since this was broaching somewhat new ground. It was determined that effectively the criteria as outlined in the pivotal protocol that that quantitation of that sort was not useful in coming up with an all or none binary answer that was meaningful.

So there wasn't, as Dr. Genant mentioned earlier, formal quantitation but there were two independent readers and I think that if there had been one little spicule, that they would not grade that as bridging trabecular bone. It would have to be meaningful but if you want further clarification, then we can get Dr. Genant back.

DR. LENCHIK: That's all right. The last question is perhaps the easiest to answer. I have read several times in the documentation that patients -- plain films were evaluated first and if they were fused by plain films then they were basically considered fused. If not, they had CT scan. Does that mean that the CT scans were not evaluated in the patients who were fused by plain films or were CT scans actually read in every single patient from whom they were obtained?

DR. BODEN: CT scans were -- this is Scott Boden. CT scans were read in every single patient. That was only the decision algorithm as to whether or not they were classified as fused.

DR. GENANT: This is Harry Genant again.